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Brief Research Communication

Nonlinkage of D6S260, a Putative Schizophrenia Locus, to Bipolar Affective Disorder

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To examine whether genes that predispose to schizophrenia also confer a predisposition to other psychiatric disorders such as bipolar affective disorder (BAD), we tested for linkage between the recently identified schizophrenia susceptibility locus D6S260 and the inheritance of BAD in 12 large Australian pedigrees. We found no evidence for linkage over a region of 12–27 cM from the D6S260 locus, depending on the model used. Our results therefore do not provide support for the continuum theory of psychosis.

KEY WORDS: **genetic predisposition, schizophrenia, bipolar affective disorder, manic depressive illness, human chromosome 6, genetic linkage analysis**

INTRODUCTION

Since Kraepelin [1921] first proposed that dementia praecox (schizophrenia) and manic depressive insanity (bipolar affective disorder and severe depression) were two distinct disorders, there has been much controversy over the relationship of these illnesses. These disorders may either lie on a continuum of psychosis [Crow, 1986] or represent distinct categorical disorders [Cloninger, 1994]. Gershon [1994] recently stated it is possible that a definitive answer may only be given once genetic markers for these diseases have been identified. If some degree of overlap exists for these diseases, then a gene (or genes) predisposing to one disorder may also predispose to the other. In view of these uncertainties, it seems prudent that loci which appear to predispose to schizophrenia should also be examined for linkage to bipolar affective disorder (BAD) and vice versa.

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RESULTS AND DISCUSSION

A susceptibility locus for schizophrenia has been reported on chromosome 6p22–25 in pedigrees from the Irish study of schizophrenia [Wang et al., 1995; Straub et al., 1995], and this finding has been replicated [Moises et al., 1995; Schwab et al., 1995]. Wang et al. [1995] reported a lod score of 3.9 for the D6S260 microsatellite marker, while Straub et al. [1995] examined four markers in this chromosomal region, and obtained a maximum lod score of 3.73 for the D6S296 marker, which is 17 cM proximal to D6S260.

To examine the continuum hypothesis, we tested for evidence of linkage between the D6S260 marker and BAD in Australian pedigrees in which no family members had either schizophrenia or schizoaffective disorder.

Twelve Australian bipolar pedigrees with unilineal inheritance (no history of BAD or recurrent major depression in marrying-in spouses or first- and second-degree relatives of each spouse) were used in this study [Le et al., 1994]. Yale-NIMH "best estimate" diagnosis consensus guidelines were used to determine final Research Diagnostic Criteria (RDC) diagnoses for bipolar I (BPI), bipolar II (BPII), and recurrent major depression (UP) from family history-RDC and structured (Schedule for Affective Disorders and Schizophrenia-Lifetime Version (SADS-L) and Composite International Diagnostic Interview (CIDI)) interview-derived RDC diagnoses [Robbins et al., 1988]. DNA was extracted from peripheral blood lymphocytes and used for genotyping the D6S260 microsatellite marker. A total of 196 individuals were genotyped, including 56 affected members. PCR amplification was undertaken as previously described [Le et al., 1994] using the primer sequences obtained from the Genome Database [Gyapay et al., 1994]. Fourteen dinucleotide alleles, ranging in size from 159–187 bp, with the exception of the 185-bp allele, were observed for the D6S260 marker in our pedigrees. Allele frequencies were calculated from 42 unrelated individuals from within the Australian pedigrees and were 0.01, 0.07, 0.11, 0.03, 0.11, 0.05, 0.07,

TABLE I. Different Modes of Inheritance, Maximum Age-Specific Penetrance Levels and Diagnostic Thresholds Investigated for Linkage Between D6S260 and Bipolar Disorder in 12 Australian Pedigrees*

Mode of inheritance	Maximum penetrance (%)	Diagnostic threshold	LOD score at θ = 0.0	Exclusion (cM)
Dominant	90	BPI	−10.5	21
Dominant	90	BPI, BPII	−11.1	19
Dominant	90	BPI, BPII, UP	−21.4	27
Dominant	60	BPI	−8.5	15
Dominant	60	BPI, BPII	−6.8	12
Dominant	60	BPI, BPII, UP	−11.1	21
Recessive	90	BPI	−10.8	17
Recessive	90	BPI, BPII	−14.6	22
Recessive	90	BPI, BPII, UP	−19.2	22
Recessive	60	BPI	−6.3	16
Recessive	60	BPI, BPII	−8.4	16
Recessive	60	BPI, BPII, UP	−8.7	16

*Diagnostic thresholds [Le et al., 1994] are bipolar I (BPI), bipolar II (BPII), and recurrent unipolar major depression (UP).

0.15, 0.11, 0.14, 0.07, 0.05, 0.01, and 0.01 for the 14 alleles in increasing size order.

Two-point linkage analyses using MLINK (Version 5.22) [Terwilliger and Ott, 1994] were undertaken by calculating lod scores, using both dominant and recessive modes of inheritance [Le et al., 1994]. Two levels of maximum age-specific penetrance were examined, 60% representing a lower estimate of the penetrance of this disorder, and 90% reflecting the high density of illness in the families under study [Le et al., 1994]. Three diagnostic thresholds, namely bipolar I (BPI), bipolar II (BPII), and recurrent unipolar major depression (UP), were used to define affection status. The disease allele frequency was taken as 0.035 (dominant) and 0.2 (recessive), and the sporadic rate was set at 0.005. The data were also examined by the affected pedigree member (APM) method [Weeks and Lange, 1988], which tests for identity by descent of disease alleles using a model-independent method.

Linkage analysis using various models of inheritance, maximum age-specific penetrance, and affection status excluded the D6S260 locus with a high degree of certainty, with lod scores of between −6.8–−21.4 being obtained at $\Theta = 0.0$ (Table I). An exclusion of linkage, based on lod scores of < -2.0, was therefore obtained for a distance of between 12–27 cM from D6S260, depending on the specific parameters used. This would also result in the exclusion of the D6S296 marker, which maps 17 cM proximal to D6S260. Results of APM analysis [Weeks and Lange, 1988] gave no support for linkage between D6S260 and BAD, at all diagnostic thresholds (Table II).

TABLE II. Affected Pedigree Member (APM) Analysis of Linkage Between D6S260 and Bipolar Disorder in 12 Australian Pedigrees*

Diagnostic threshold	APM statistic	*P* value
BPI	−0.80	0.8
BPI, BPII	−0.86	0.8
BPI, BPII, UP	−0.80	0.8

*APM statistic was calculated using the weighting function f(p) = 1/square root p, where p = allele frequency and *P* = probability.

These results indicate that there is no linkage between the D6S260 locus and BAD in the 12 pedigrees examined, and hence that the basis for genetic susceptibility in these families is clearly distinct from that for schizophrenia in the Irish study. Our data therefore do not provide evidence in support of the continuum theory [Crow, 1986]. The likelihood of genetic heterogeneity in the etiology of both schizophrenia and BAD means that similar studies will have to be undertaken with each newly reported candidate susceptibility locus to establish that these conditions are distinct disorders.

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